

## Lecture 1 Base Catalyzed Reactions I

### 1.1 Principles

The base catalyzed carbon-carbon bond formation is closely related to the carbon-carbon bond formation from organometallic reagents. In both methods, the negatively polarized carbon reacts with electrophilic carbon of carbonyl groups and related compounds.

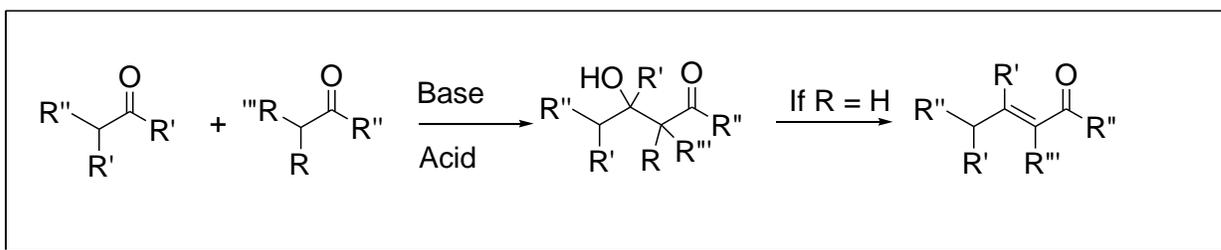
The scope of the base-catalyzed reactions depends on three facts: (i) a wide range of organic compounds is able to form carbanions, (ii) these carbanions undergo reaction with electrophilic carbon in a variety of environments, and (iii) the basicity of the reagent used to abstract the proton may be widely varied.

### 1.2 Reactions of Enolates with Carbonyl Compounds

#### 1.2.1 Reactions with Aldehydes and Ketones

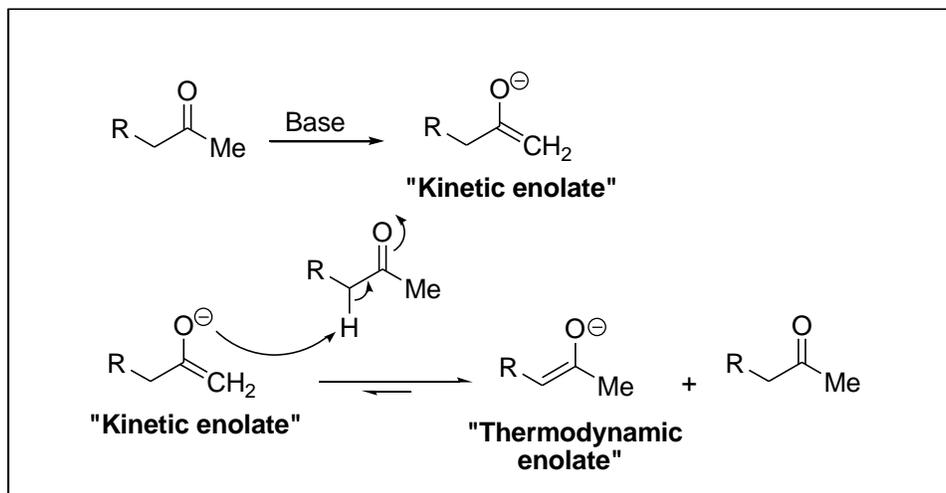
##### 1.2.1.1 Aldol Condensation

The reaction has become one of the most important methods for carbon-carbon bond formation. It consists of the reaction between two molecules of aldehydes or ketones that may be same or different. One of the reactants is converted into a nucleophile by forming its enolate in the presence of base and the second acts as an electrophile (Scheme 1).



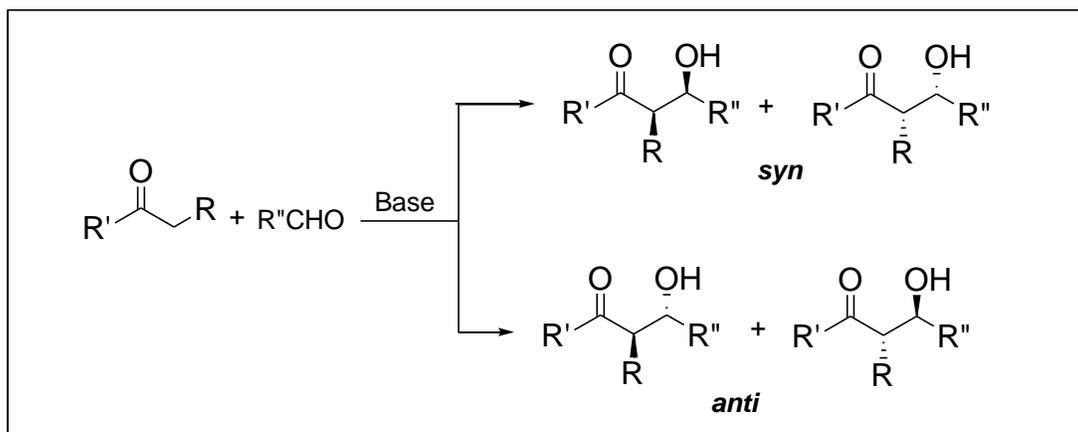
Scheme 1

The geometry ((*Z*)- or (*E*)) of the enolate depends on the reaction conditions and the nature of the substituents. Strong base (e.g. LDA), low temperature and short reaction time lead to *kinetic enolate*, while weak base (e.g. hydroxide ion), high temperature and longer reaction time favour the formation of *thermodynamic enolate* (Scheme 2)



Scheme 2

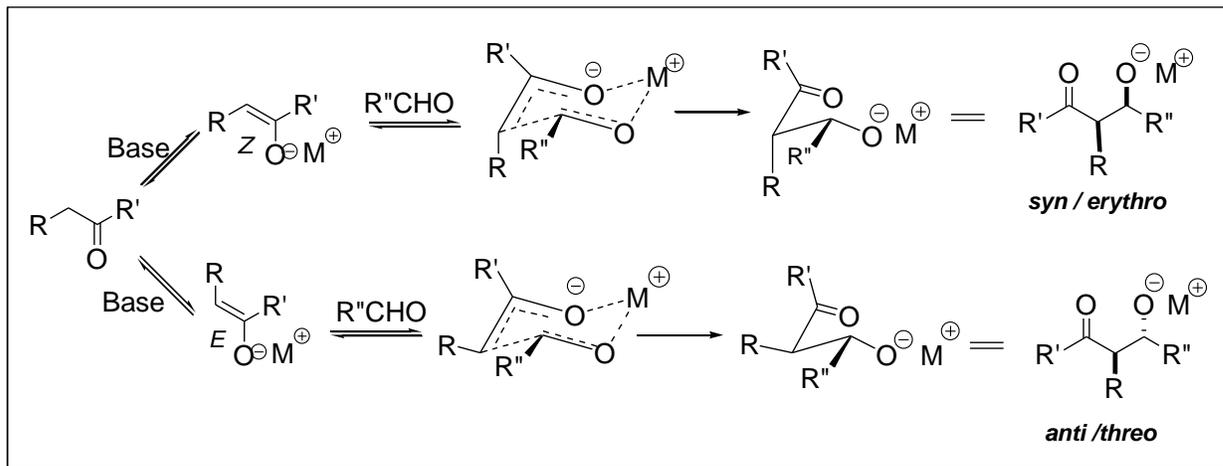
If the reactants are not the same, they can lead to the formation of diastereoisomers and their distribution depends on the reaction conditions and the nature of the substituents (Scheme 3).



Scheme 3

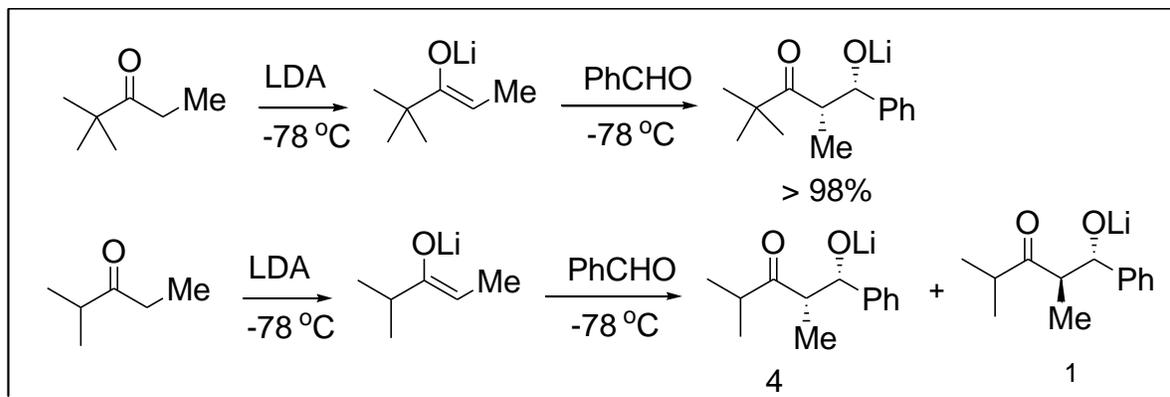
Under thermodynamic control, the (*Z*)- and (*E*)-forms of the enolates are in rapid equilibrium, and the product distribution is determined by the relative stabilities of the six-membered chair-shaped cyclic transition states that includes the metal counter-ion (Scheme 4). Transition state that leads to the *syn* product has  $R$  in the less stable axial position, whereas in that leading to *anti* product both  $R$  and  $R'$  are in the more stable

equatorial position. The latter is therefore of lower energy, leading to a major *anti* product.



Scheme 4

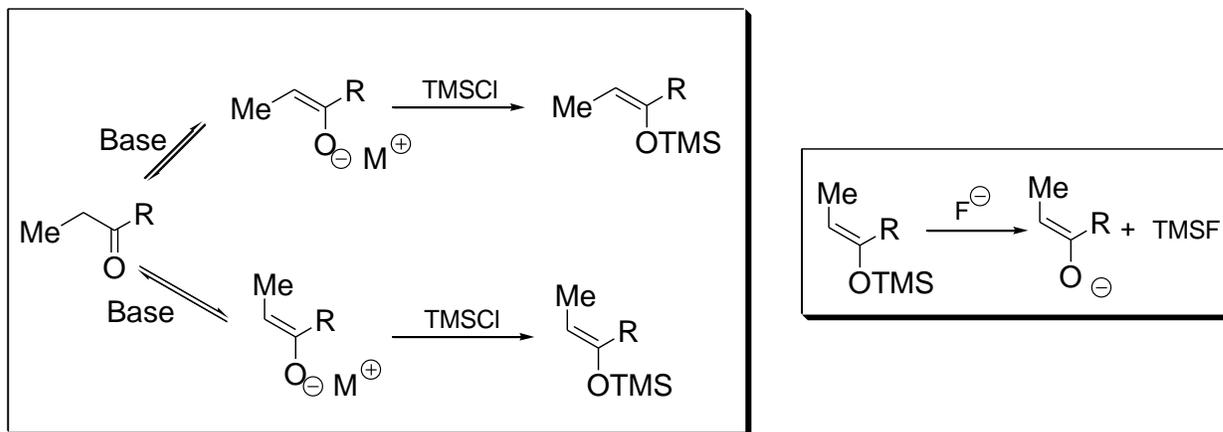
In contrast, under kinetic control, the (*Z*) and (*E*) enolates are formed rapidly and irreversibly, and their relative amounts determine the product distribution (Scheme 5). For examples, for ketone  $\text{CH}_3\text{CH}_2\text{CO}^t\text{-Bu}$ , the (*Z*)-enolate is normally formed to afford the *syn* diastereoisomer as a



Scheme 5

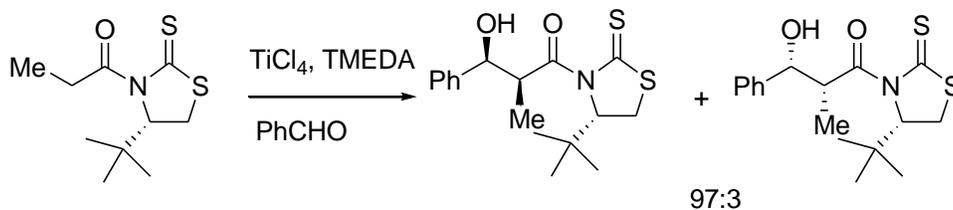
major product. But, the selectivity falls to 4:1 (*syn:anti*) when the size of the R is reduced from *t*-Bu to isopropyl. This is presumably because of the difference in steric repulsion of the methyl group with *t*-butyl and isopropyl groups.

However, there is a general technique to increase the degree of diastereoselectivity. The enolate can be converted into silyl enol ethers that can be separated by distillation. The separated silyl enol ethers can then be converted into pure (*Z*)- or (*E*)-enolate by treatment with fluoride ion (Scheme 6).

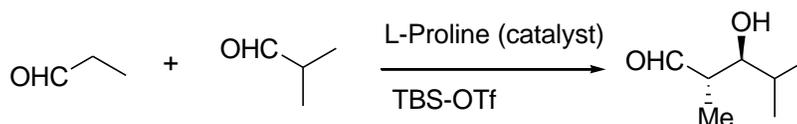


Scheme 6

Asymmetric version of this reaction has also been well explored. For examples, chiral auxiliaries and chiral catalysts have been used as chiral source for asymmetric aldol reactions (Scheme 7).



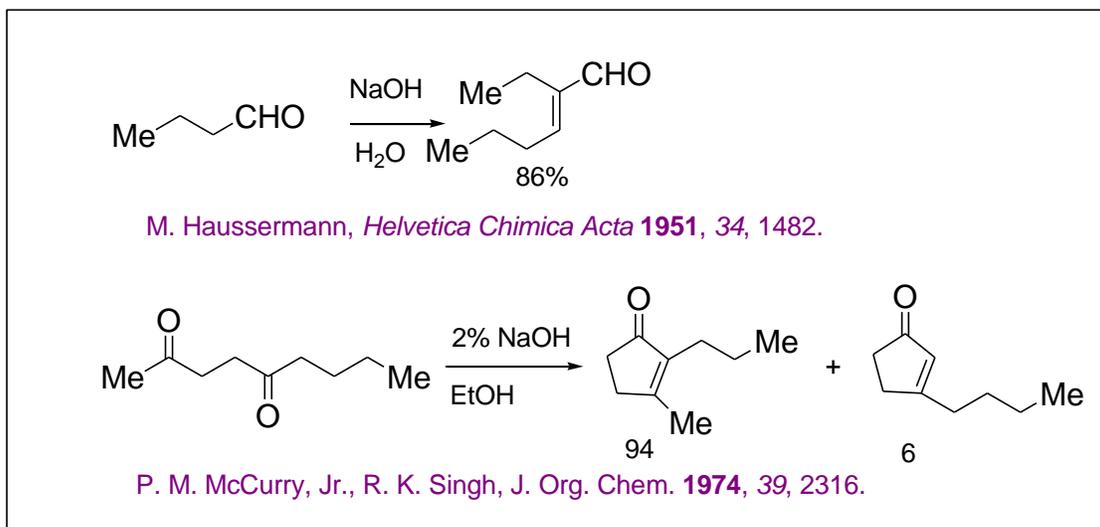
M. T. Crimmins, K. Chaudhary, *Org. Lett.* **2000**, *2*, 775.



P. M. Pihko, A. Erkkila, *Tetrahedron Lett.* **2003**, *44*, 7607.

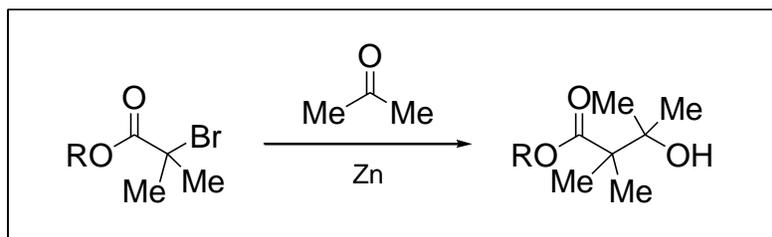
Scheme 7

**Examples:**

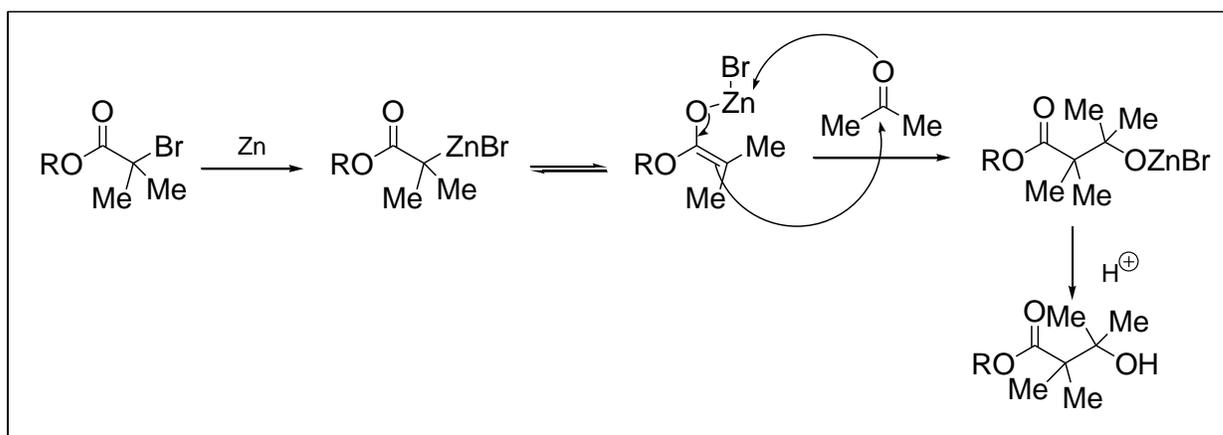


1.2.1.2 The Reformatsky Reaction

The enolate generated from an  $\alpha$ -bromo ester with zinc reacts with an aldehyde or ketone to give an aldol-type product in diethyl ether (Scheme 8).

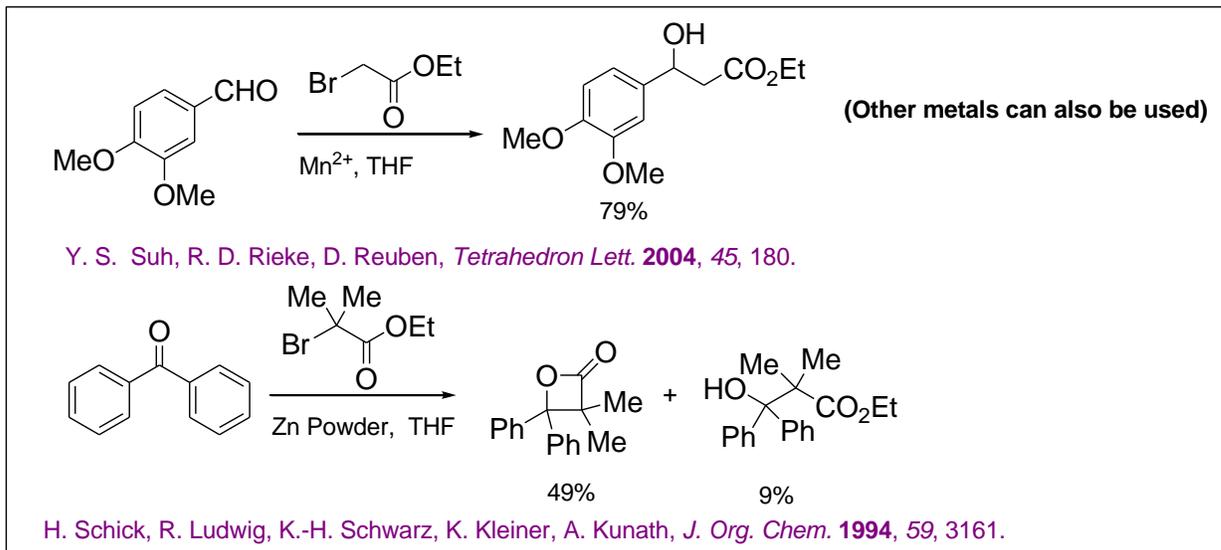


**Mechanism**



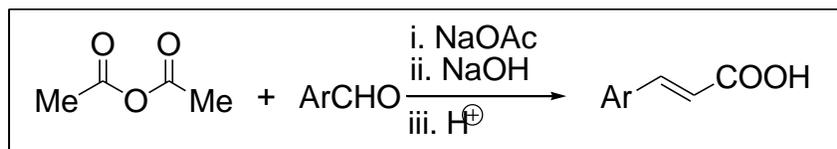
Scheme 8

**Examples:**

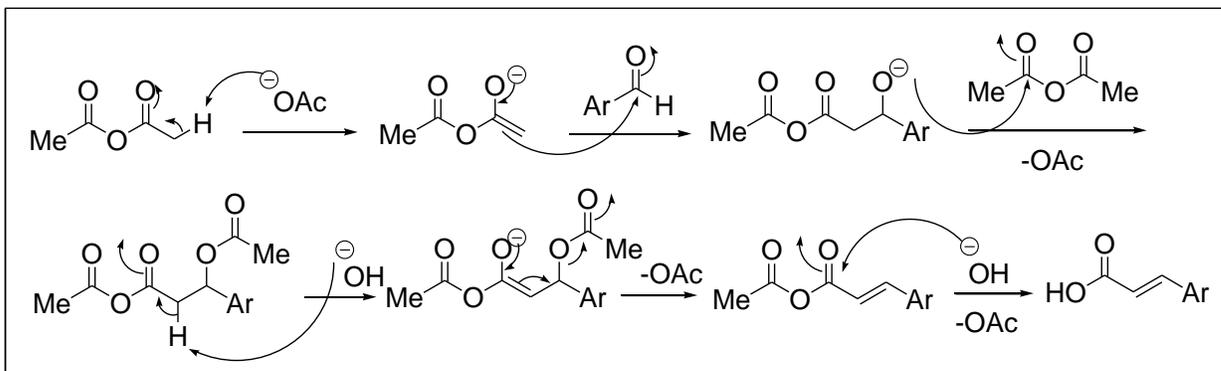


**1.2.1.3 The Perkin Reaction**

This process consists of the condensation of an acid anhydride with an aromatic aldehyde using carboxylate ion (Scheme 9).



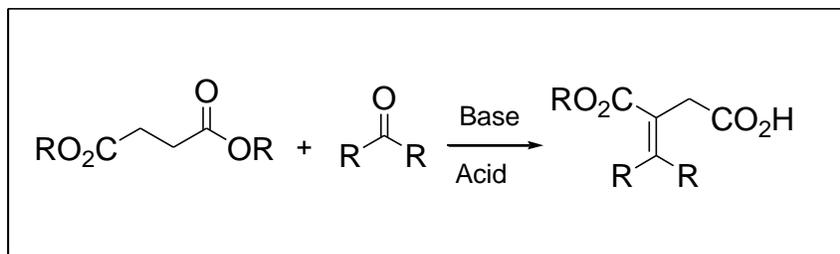
**Mechanism**



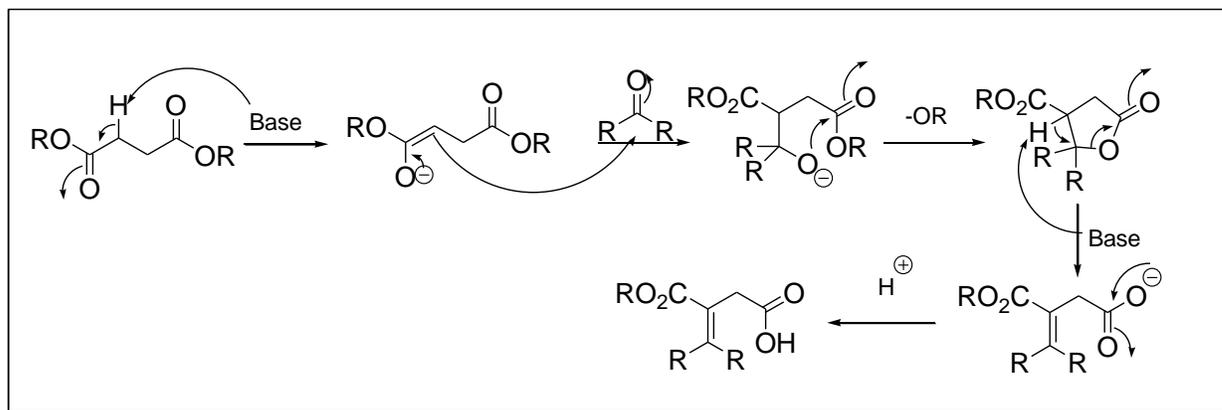
Scheme 9

### 1.2.1.4 The Stobbe Condensation

The Stobbe condensation leads to attachment of three carbon chain to a ketonic carbon atom (Scheme 10).

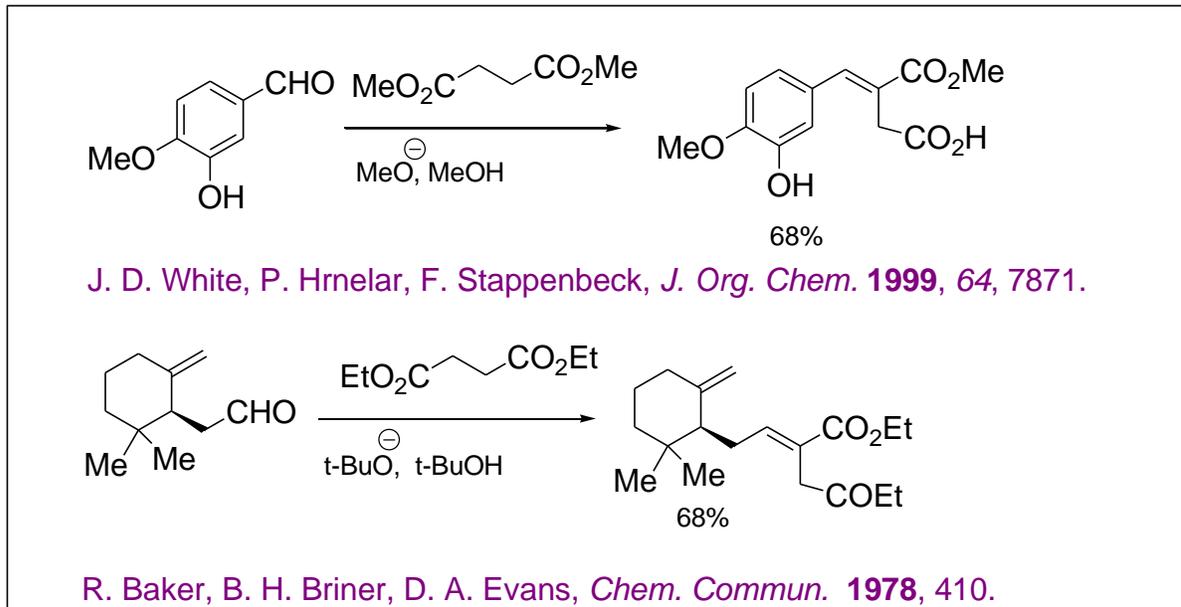


#### Mechanism



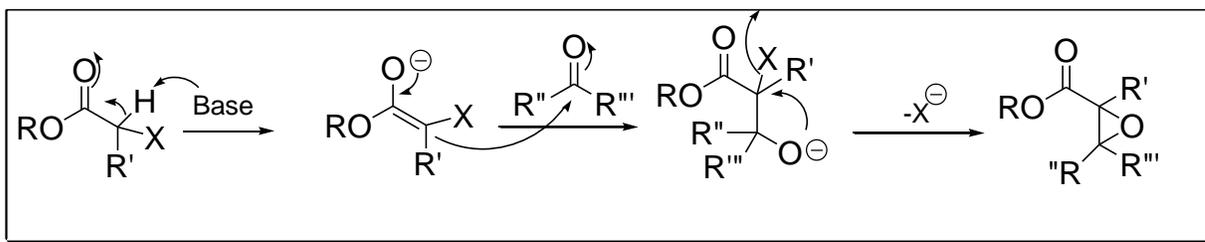
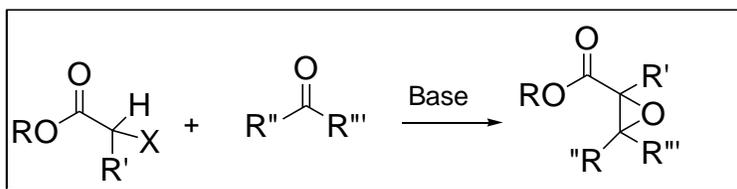
Scheme 10

**Examples:**

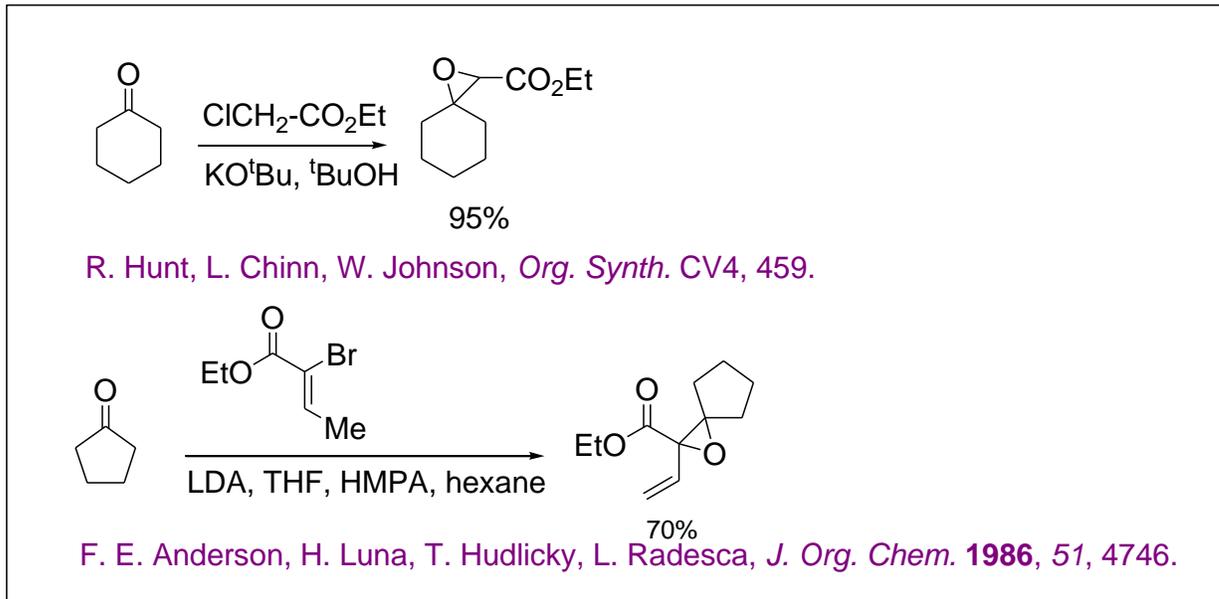


1.2.1.5 The Darzen Reaction

The base-catalyzed condensation between an  $\alpha$ -halo ester and an aldehyde or ketone affords glycidic ester (Scheme 11).

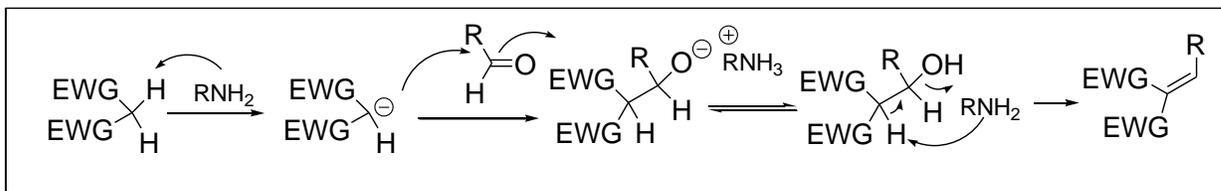
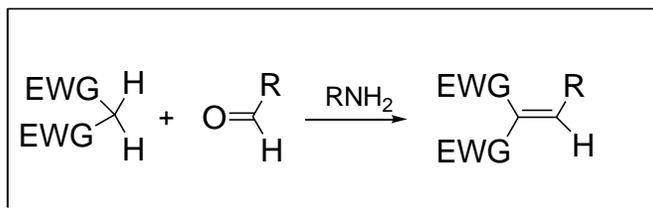


Scheme 11

**Examples:**


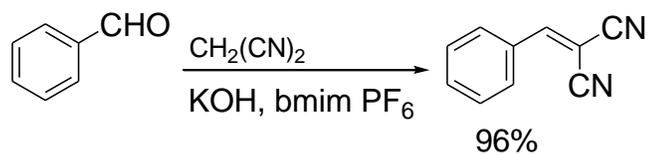
## 1.2.1.6 The Knoevenagel Reaction

The condensation of methylene group bonded with two electron withdrawing groups with aldehydes or ketones using weak base is known as the Knoevenagel reaction (Scheme 12). The reaction is more useful with aromatic than with aliphatic aldehydes.

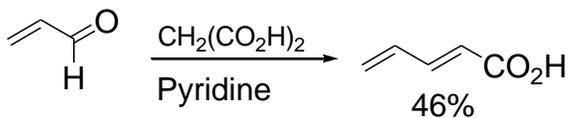


Scheme 12

**Examples:**



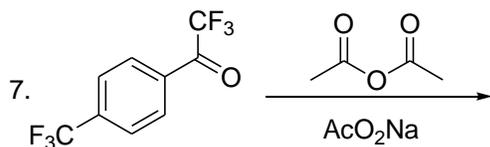
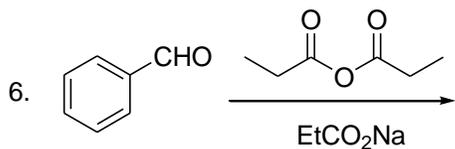
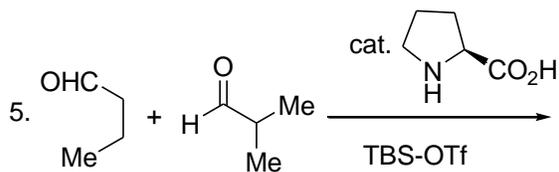
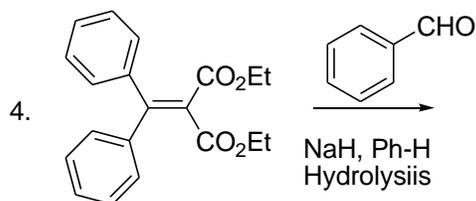
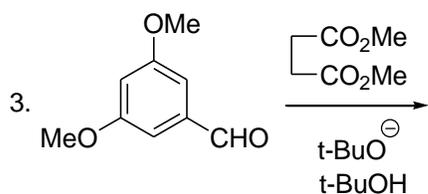
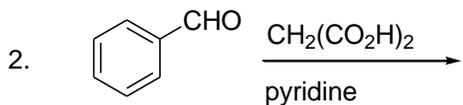
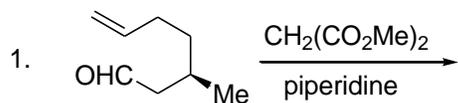
P. Formentin, H. Garcia, A. Leyva, *J. Mol. Catal. A: Chem.* **2004**, 214, 137.



P. J. Jessup, C. B. Petty, J. Roos, L. E. Overman, *Org. Synth.* CV6, 95.

**Problems:**

What products would you expect from the following reactions? Provide mechanism.



**Text Books:**

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

B. P. Mundy, M. G. Ellerd, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.

J. March, *Advanced Organic Chemistry*, 4<sup>th</sup> ed, Wiley Interscience, New York, 1992.

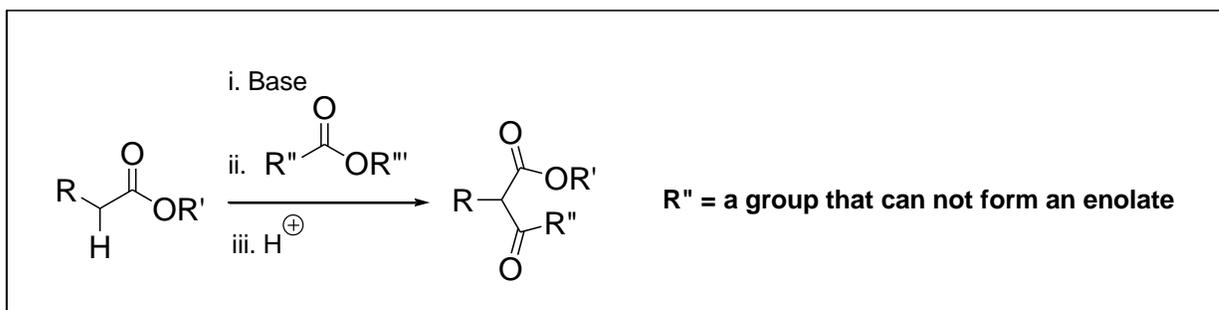


## Lecture 2 Base Catalyzed Reactions II

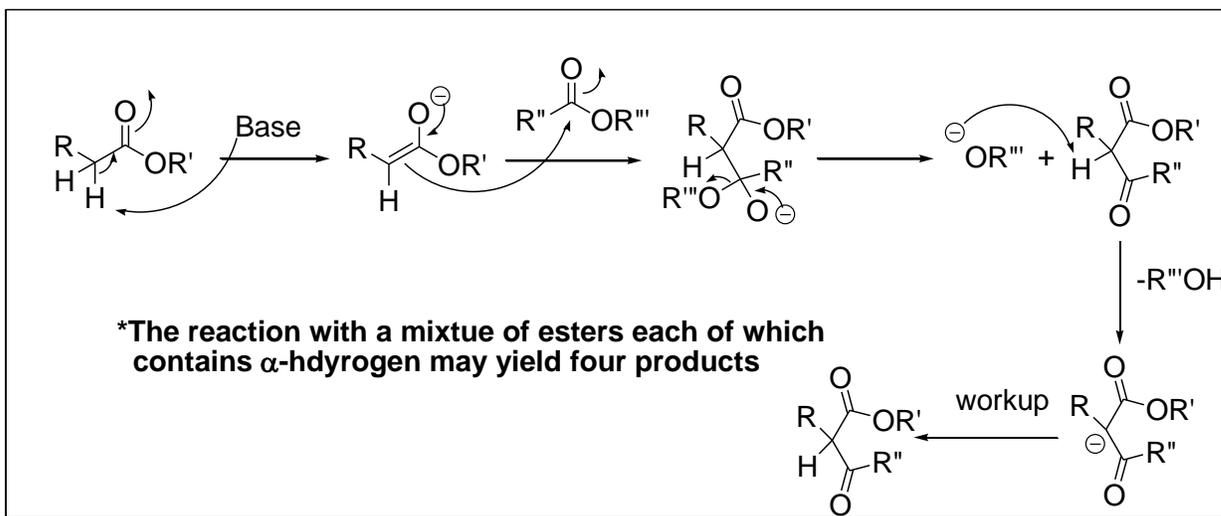
### 1.2.2 Reactions with Esters and Analogues

#### 1.2.2.1 The Claisen Condensation

The condensation of between esters is known as the Claisen condensation. It is important to note that an equivalent amount of base must be employed for this reaction (Scheme 1).

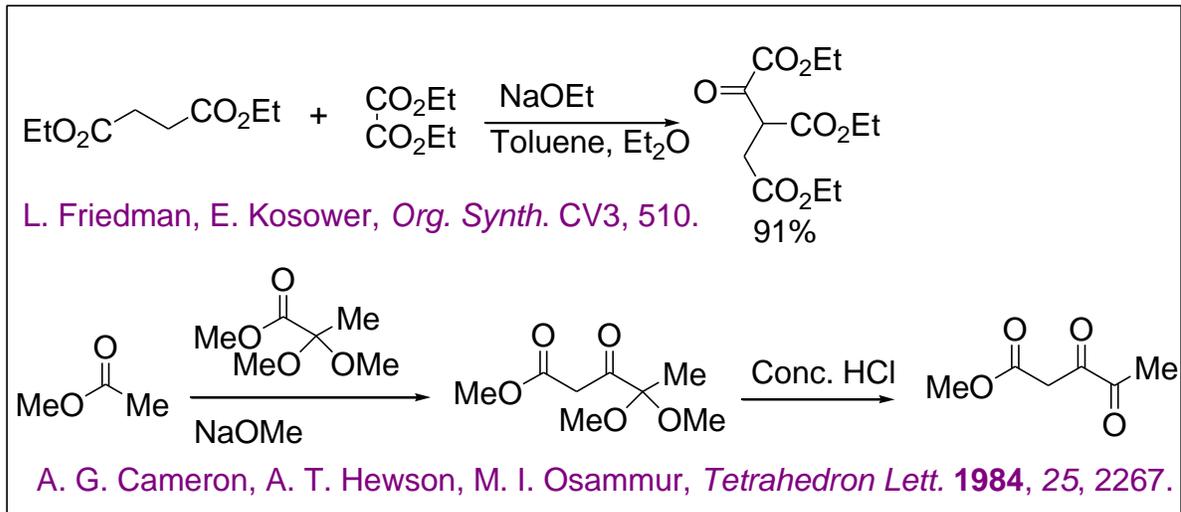


#### Mechanism



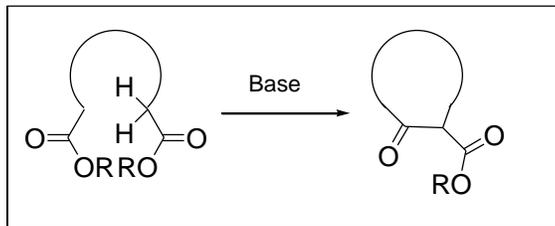
Scheme 1

**Examples:**

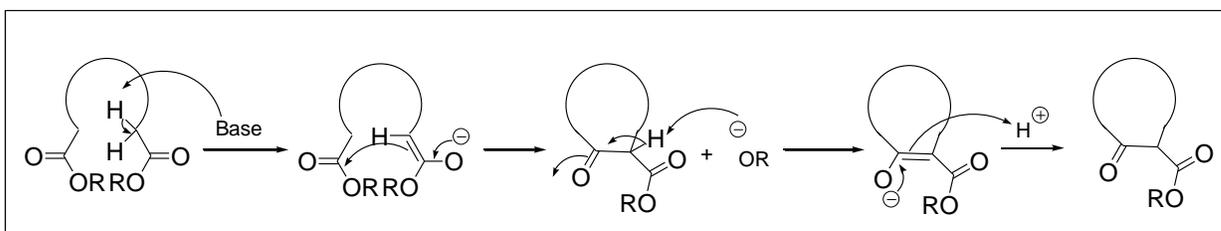


1.2.2.2 Dieckmann Condensation

Condensation of the diesters of having C<sub>6</sub> and C<sub>7</sub> can be accomplished to afford five and six membered cyclic β-ketoesters (Scheme 2). The diesters of short-chain do not show cyclization, while diesters with C<sub>8</sub> and C<sub>9</sub> provide the cyclized products in fewer yields.

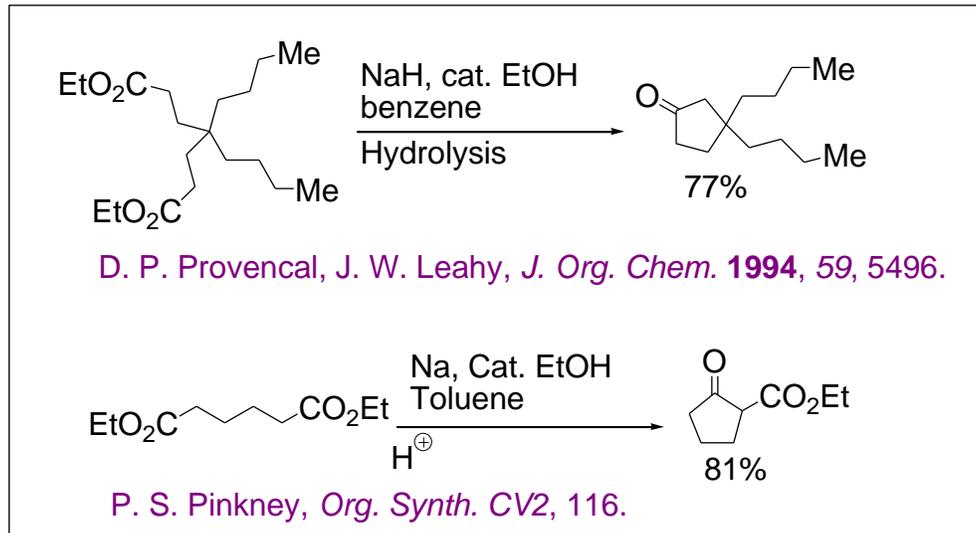


**Mechanism**



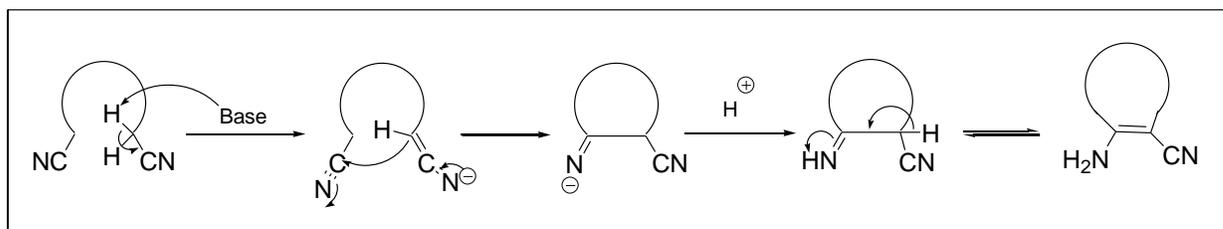
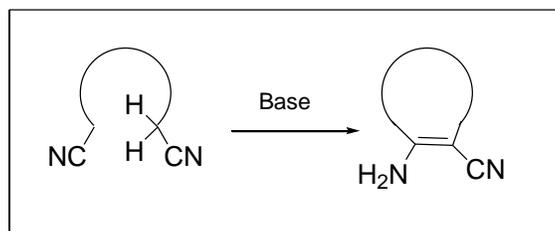
Scheme 2

**Examples:**

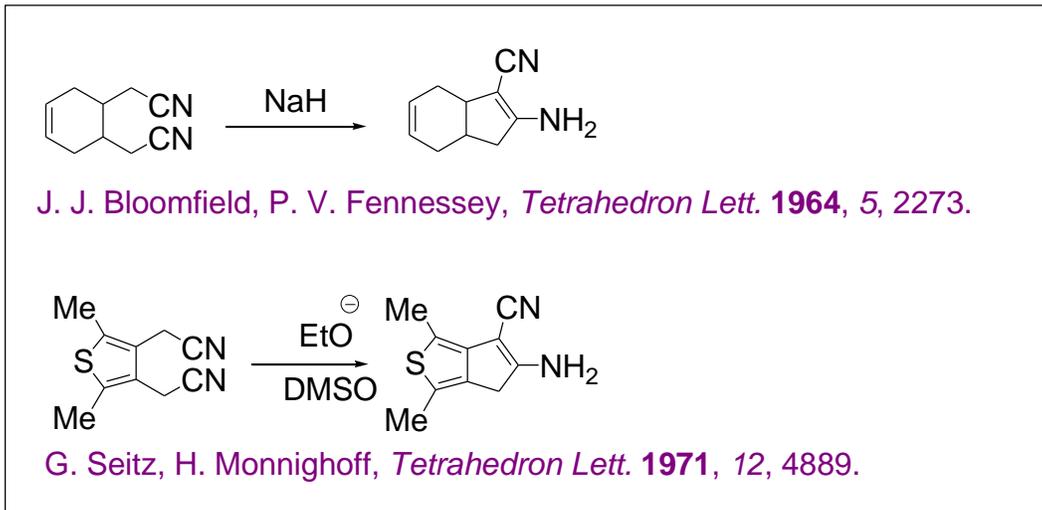


1.2.2.2 The Thorpe-Ziegler Reaction

The cyclization of dinitriles using base can be accomplished (Scheme 3). Although it is similar to the Dieckmann reaction, the former is often better compared to the latter.

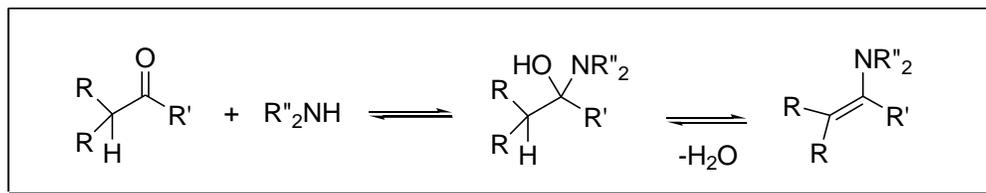


Scheme 3

**Examples:**


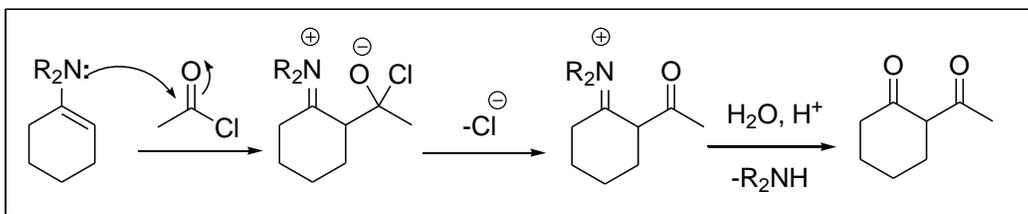
## 1.2.2.3 Enamines

The reaction of secondary amine with aldehyde or ketone that contains an  $\alpha$ -hydrogen atom affords enamine (Scheme 4). The process is driven to right by removing the water as it is formed, either by azeotropic distillation or with molecular sieves.



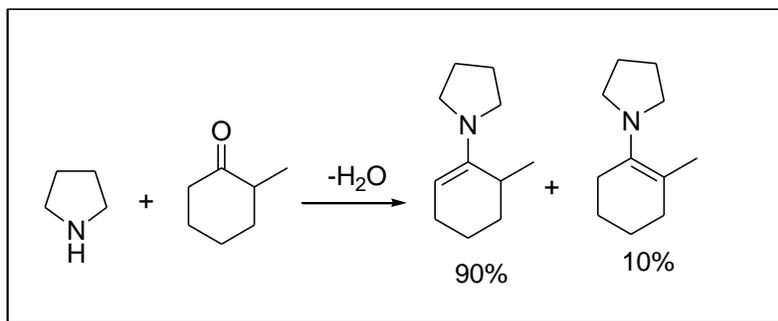
Scheme 4

Similar to the enolates derived from ketones, enamines react with acid chlorides to give imine derivative that could be hydrolyzed to  $\beta$ -diketones (Scheme 5).



Scheme 5

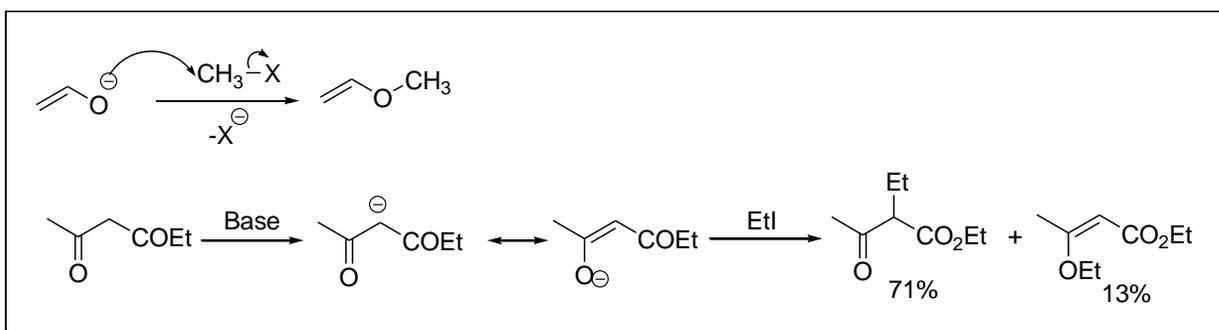
In case of unsymmetrical ketones, less substituted enamine forms as a major product (Scheme 6).



Scheme 6

### 1.3 The Alkylation of Enolates

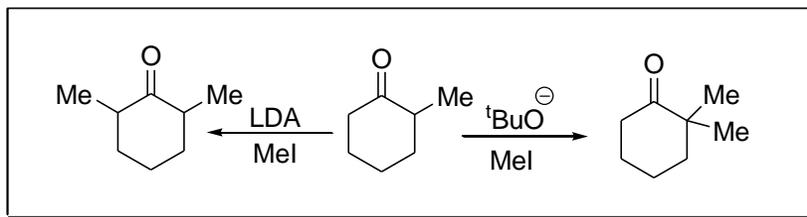
Enolates, like other nucleophiles, also undergo reaction with alkyl halides and sulfonates with the formation of carbon-carbon bonds. Depending on the reaction conditions and nature of the substrates, the reaction can occur either at oxygen atom or carbon atom of enolate (Scheme 7).



Scheme 7

### 1.3.1 Alkylation of Monofunctional Compounds

Depends on the reaction conditions (kinetic vs thermodynamic control), enolate can be selectively alkylated (Scheme 8).

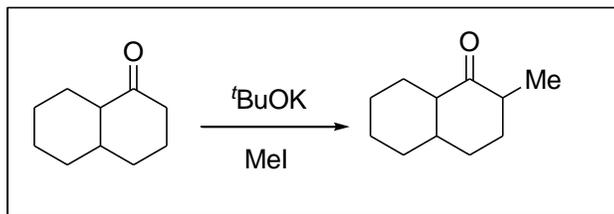


Scheme 8

*Kinetic control with LDA:* Proton abstraction takes place at less hindered  $\alpha$ -CH position and the reaction is faster and essentially irreversible.

*Thermodynamic control with  $t\text{BuOK}$ :* equilibration takes place between the two enolates and the methyl-substituted one, being the more stable, is present in high concentration.

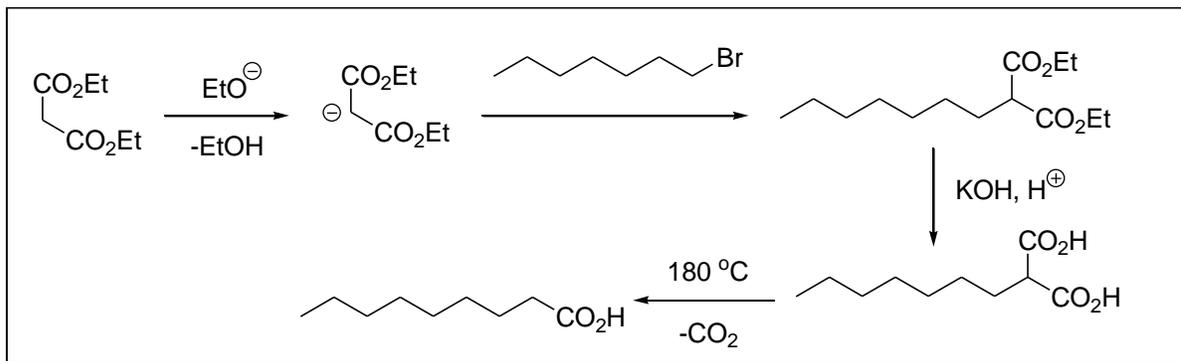
However, when the highly substituted position is strongly sterically hindered, alkylation with  $t\text{BuOK}$  occurs at the less sterically substituted carbon (Scheme 9).



Scheme 9

### 1.3.2 Alkylation of Bifunctional Compounds

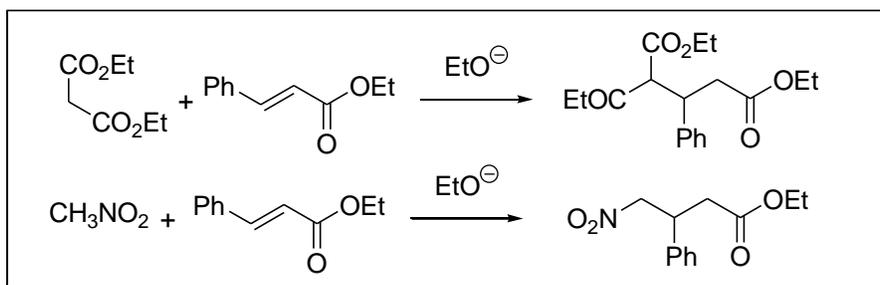
A C-H bond adjacent to two electron withdrawing groups is more acidic than that adjacent to one electron withdrawing group and the alkylation could be carried out in milder conditions (Scheme 10).



Scheme 10

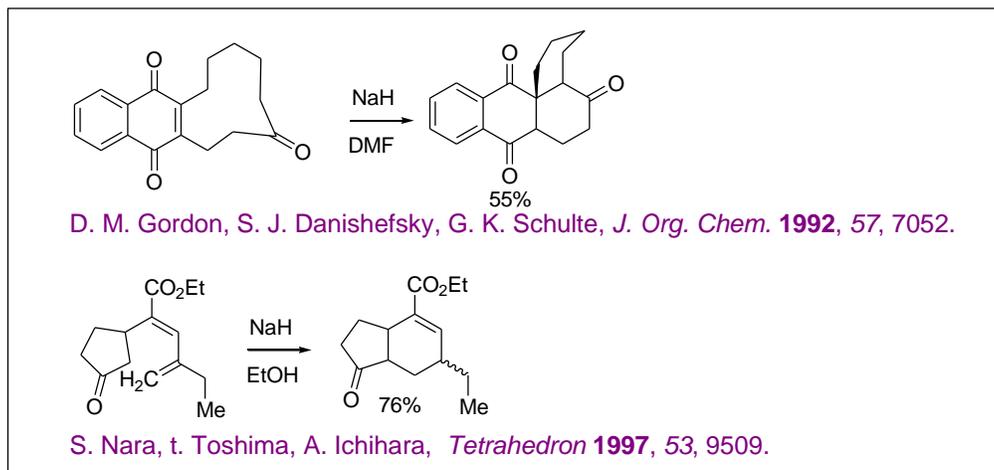
### 1.4 Addition of Enolates to Activated Alkenes

Enolates undergo addition to alkenes that are activated by conjugation to carbonyl, ester, nitro and nitril groups (Scheme 11). These reactions are usually referred to as Michael addition.



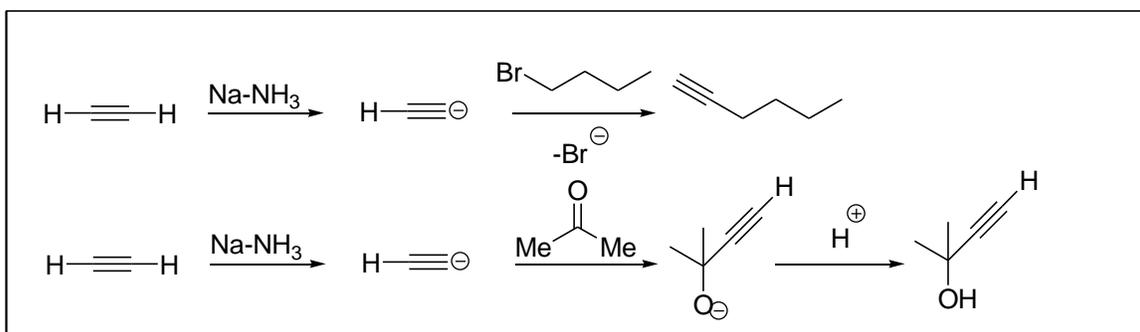
Scheme 11

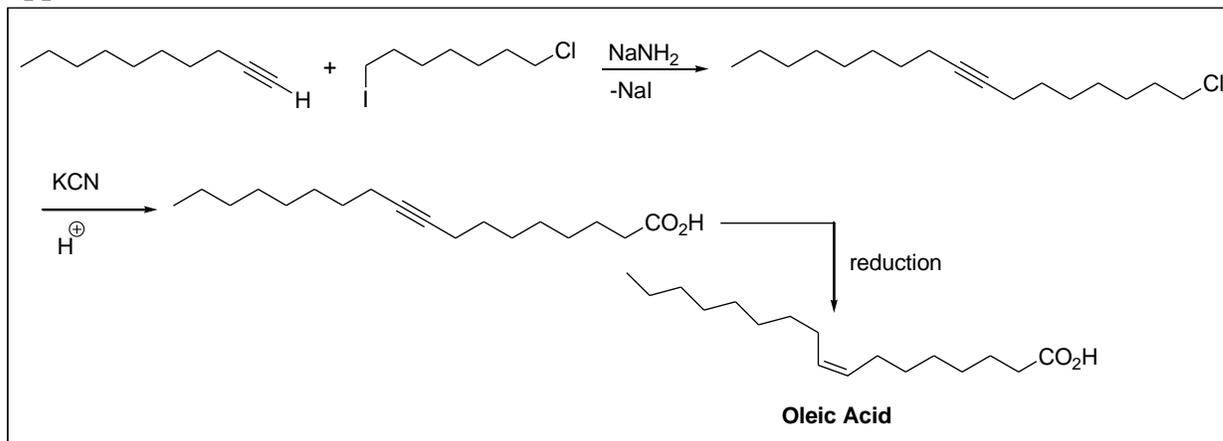
**Examples:**



**1.5.1 Reactions Involving Alkynes**

Acetylene and its monosubstituted derivatives are more acidic than alkenes and alkanes and take part in reactions with both carbonyl-containing compounds and alkyl halides in the presence of base (Scheme 12).

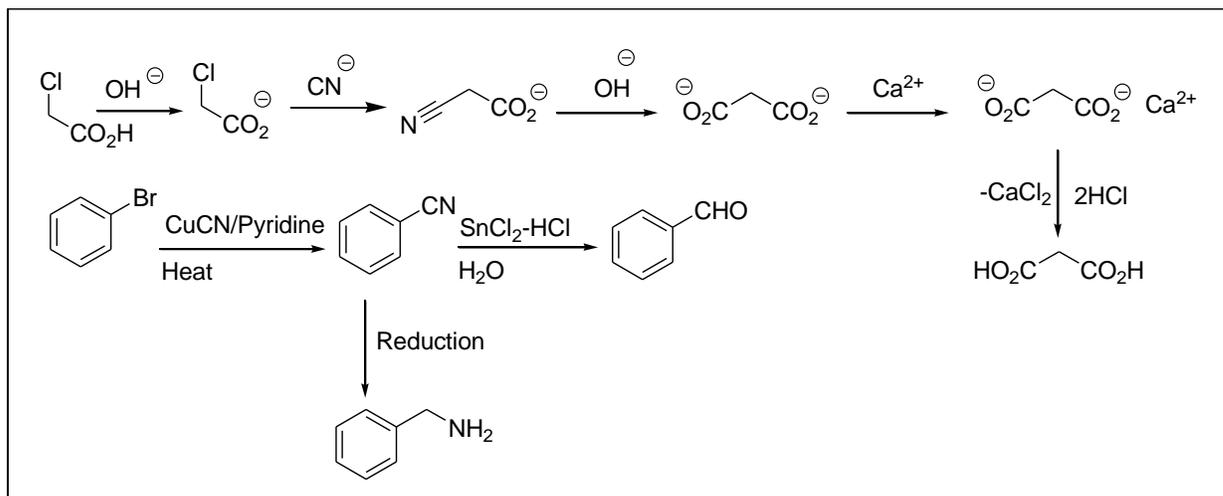


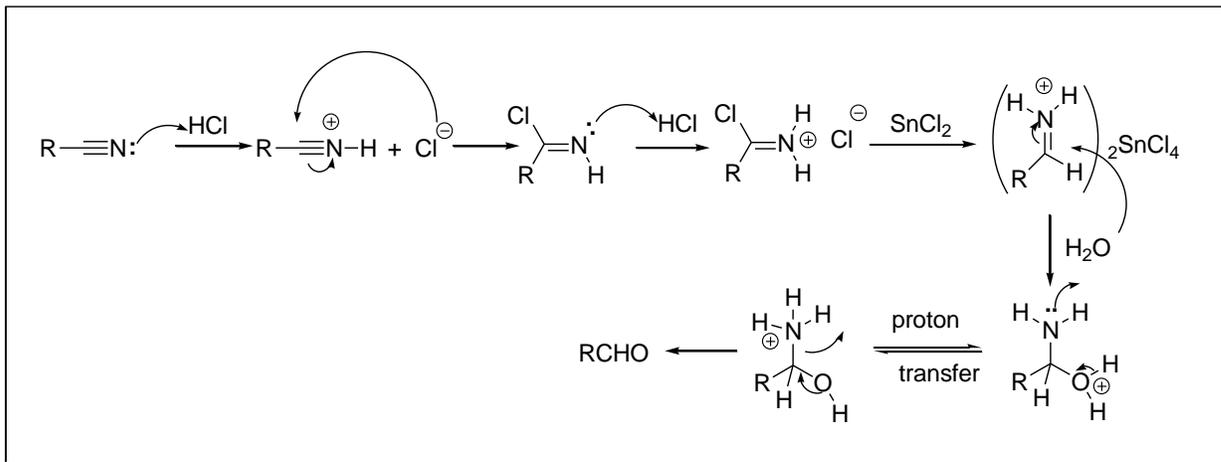
**Application**

Scheme 12

**1.5.2 Reactions of Cyanides with Alkyl Halides and Sulfonates**

$\text{HCN}$ , like acetylene, is a weak acid whose anion may be generated by base and is reactive towards primary and secondary alkyl halides and sulfonates to give the corresponding nitriles. It is more convenient to introduce the cyanide as cyanide ion (e.g.  $\text{NaCN}$ ,  $\text{TMSCN}$ ) rather than as  $\text{HCN}$ . These reactions provide a way of extending aliphatic carbon chains by one carbon atom. Scheme 13 summarizes some of the useful transformations.

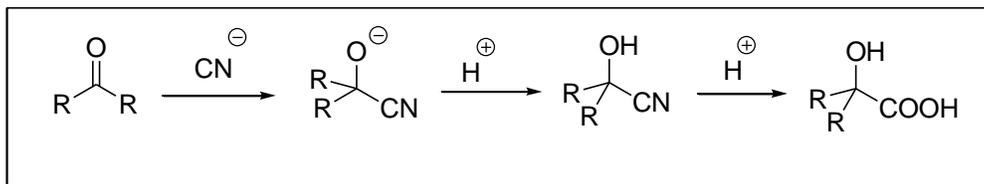


**Mechanism for Stephen Aldehyde Synthesis (Stephen Reduction)**

Scheme 13

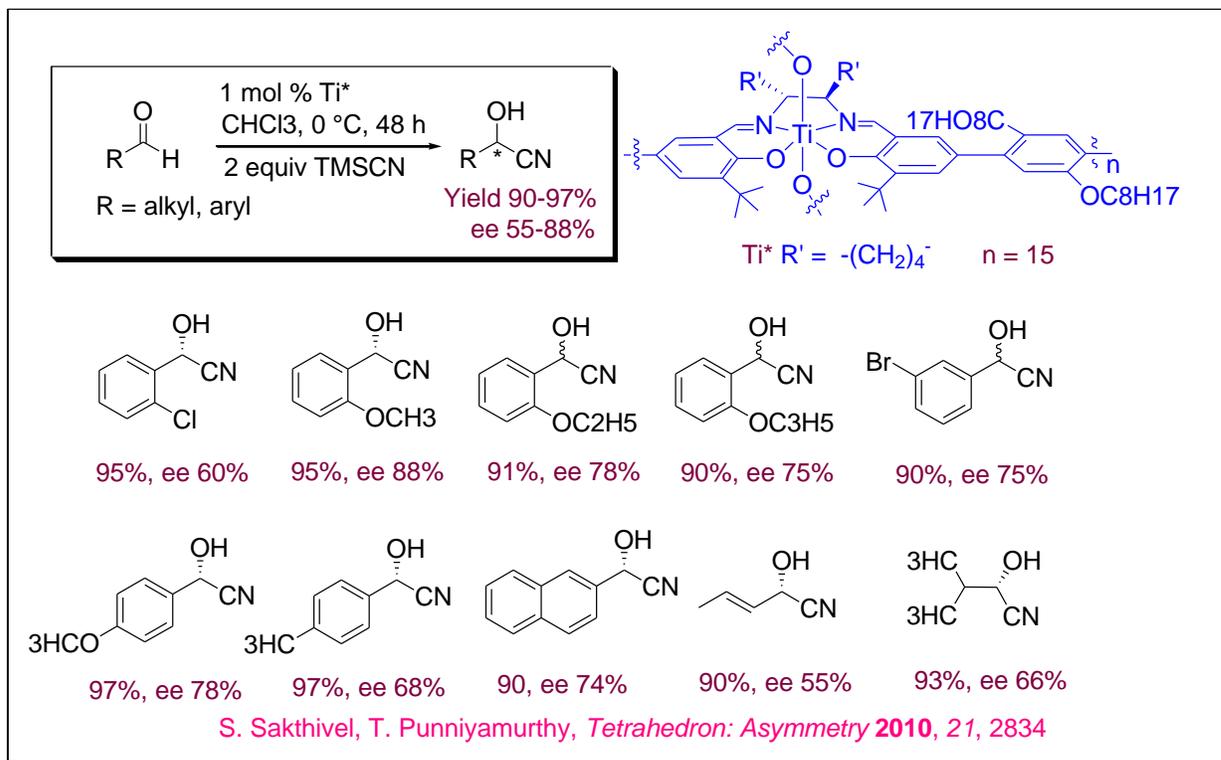
**1.2.2.5.2.2 Reactions of Cyanides with Carbonyl Compounds**

Cyanide ion adds to aldehydes and ketones to give cyanohydrins that can be hydrolyzed to  $\alpha$ -hydroxy acids (Scheme 14).



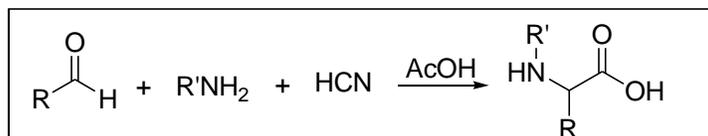
Scheme 14

Asymmetric version of the process is also well explored. For example, chiral main chain polymer having  $Ti(VI)$  has been found to be an effective recyclable catalyst to obtain the cyanohydrin with up to 88% ee (Scheme 15).

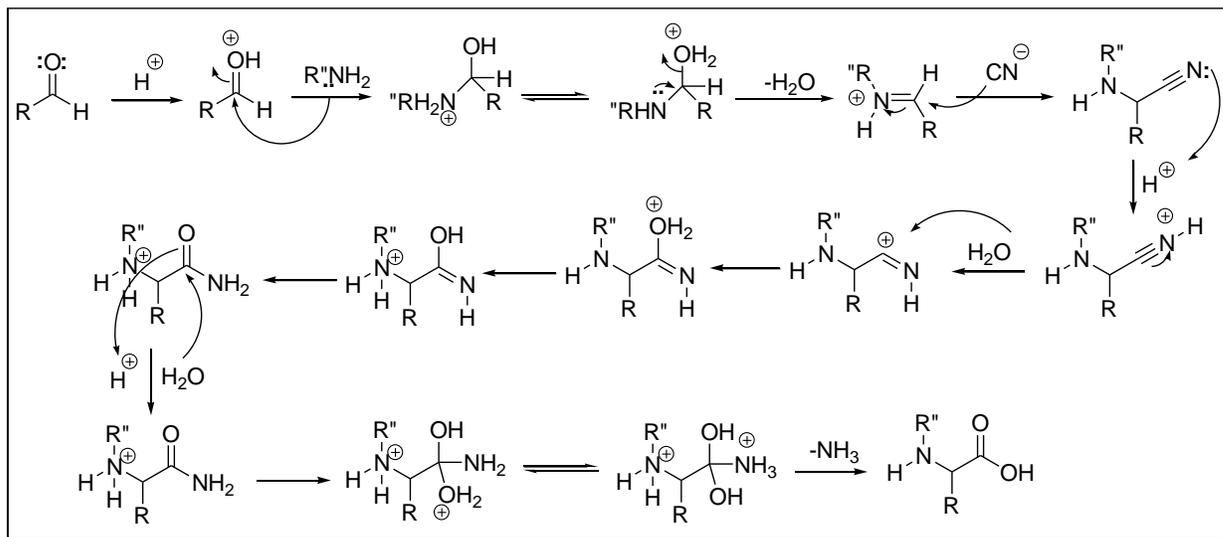


Scheme 15

Imine that can be prepared from amine and aldehyde readily undergoes reaction with cyanide ion to give  $\alpha$ -amino nitrile which can be hydrolyzed to  $\alpha$ -amino acid (Strecker synthesis) (Scheme 16).

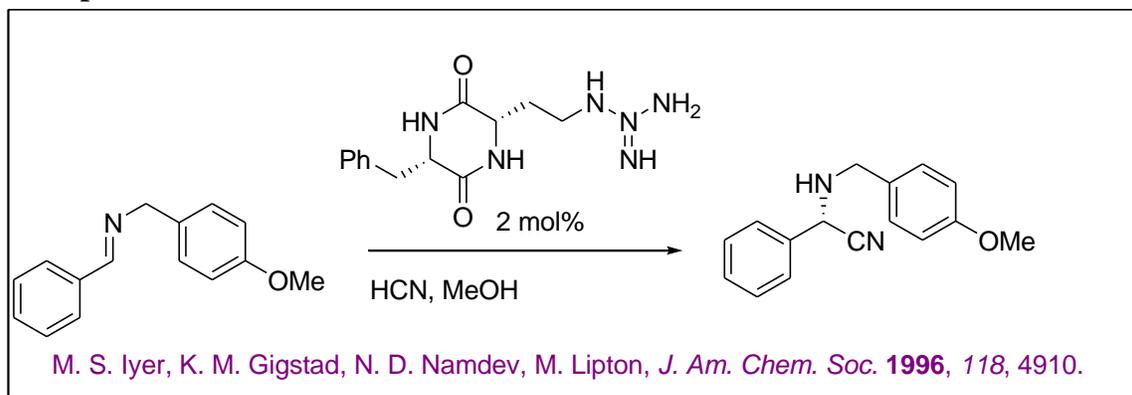


## Mechanism



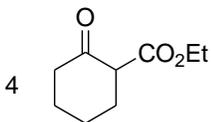
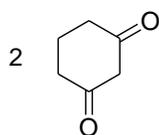
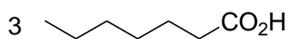
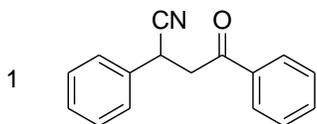
Scheme 16

## Example:

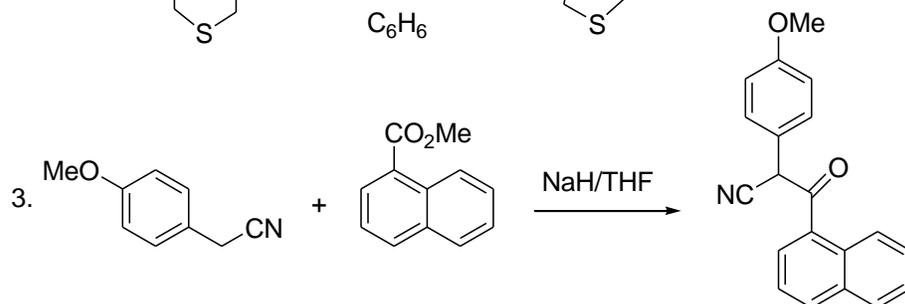
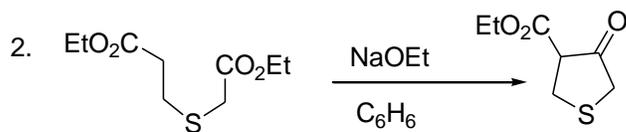
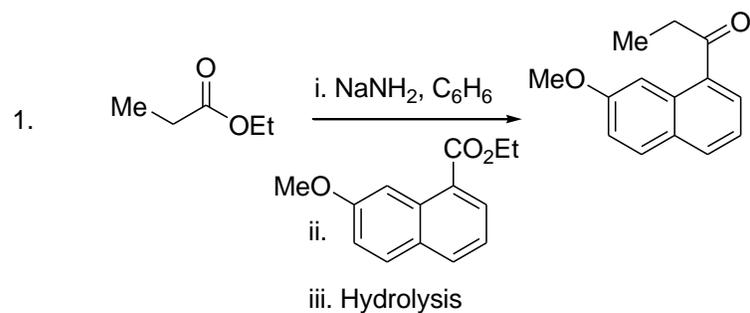


## Problems:

A. How would you use base-catalyzed reactions in the synthesis of the following compounds?



**B. Rationalize the following reactions.**



**Text Books:**

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

B. P. Mundy, M. G. Ellerd, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.

J. March, *Advanced Organic Chemistry*, 4<sup>th</sup> ed, Wiley Interscience, New York, 1992.

